Nonprostate Urologic Oncology

Therapeutic Strategies, Predicting Outcomes in Patients With Renal Cell and Transitional Cell Carcinomas

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The search continues for more effective treatments for patients with renal cell carcinoma (RCC), with immunotherapy currently showing promise. For patients with advanced RCC, survival predictors can help clinicians to stratify patients. Postchemotherapy surgery to resect residual cancer in patients with transitional cell carcinoma (TCC) may be an option for carefully selected patients.

Up-Regulation of Retinoic Acid Receptor ß Expression in Renal Cancers *In Vivo* Correlates With Response to 13-*cis*-Retinoic Acid and Interferon-α-2a.

Berg WJ, Nanus DM, Leung A, et al.
Clin Cancer Res. 1999;5:1671-1675.

The inefficacy of surgery, radiation therapy, hormonal therapy, and chemotherapy in altering the dismal natural history of advanced and metastatic RCC has stimulated the search for more effective approaches. Biologic strategies using immunotherapy are the only current treatments that have produced promising therapeutic results. The authors of this study from Memorial Sloan-Kettering Cancer Center (MSKCC) have published their results previously using the combination of 13-*cis*-retinoic acid (13-CRA) and interferon alpha (IFN-α), which demonstrated improved response rates, suggesting that 13-CRA potentiates the antitumor effects of IFN-α. The mediators of retinoic acid biologic activity include a family of several retinoic acid receptors (RAR) isoforms, and expression of specific retinoid receptor messenger RNA (mRNA) has been shown to suppress the growth of malignant leukemia, breast cancer, lung cancer, and teratocarcinoma lines. The authors have also shown previously that the only known retinoid-sensitive RCC cell line, SK-RC-06, basally expressed RAR-ß and that RAR-ß mRNA expression was up-regulated by 13-CRA treatment. In the current study, the authors sought to determine whether RAR-ß mRNA expression in vivo could predict response to retinoid-based therapy in patients studied in a phase II trial of 13-CRA and IFN-α.

Forty-five patients with advanced RCC were treated with both oral 13-CRA at a dosage of 1 mg/kg/d and subcutaneous injections of IFN-α with dose escalation to 9 million units daily. Response criterion for a major response was defined as a greater than 50% decrease in the summed products of the perpendicular diameters of all measured lesions for a minimum of 4 weeks. Renal cancer specimens were obtained from 23 patients prior to the clinical trial; then, 10 specimens were obtained from patients on active therapy or within 1 month of discontinuing treatment. RAR-ß mRNA expression was then determined using nonradioactive in situ hybridization. Specimens were categorized by the pretreatment level of RAR-ß mRNA expression and by the change in relative staining of the expression with treatment. The relationship between expression and treatment response was assessed using the two-sided Fisher's exact test.

RAR-ß expression was present in 22 (96%) of 23 pretreatment specimens and in 9 (90%) of 10 specimens from treated patients. Pretreatment levels of expression were not predictive of major clinical response to RA plus IFN-α therapy. However, an increase in the intensity of RAR-ß mRNA expression was detected in 4 (80%) of 5 patients who achieved a major response but in 0 of 5 patients whose disease progressed and for whom sequential tissue specimens were available.

Although this study involves a small number of patients and is limited by having to compare pre- and post-treatment RAR-ß mRNA expression from different tumor sites in the same patients, the data presented have interesting implications regarding the possible mechanisms of coop-

eration between 13-CRA and INF. First, pretreatment levels of RAR-ß cannot be used as a marker to select patients with advanced RCC for retinoid-based therapies. Second, patients whose tumor cells were able to increase their expression of RAR-ß experienced a clinical response, while those whose tumor cells were unable to do this did not. This supports the concept that RAR-ß is a mediator for the antitumor effect of RA on RCC. Taken together, this study provides the rationale for the concept that further studies of agents that can induce RAR-ß expression should be performed and that these agents may hold some promise for the future of immunotherapy in the management of advanced or metastatic RCC.

Survival and Prognostic Stratification of 670 Patients With Advanced Renal Cell Carcinoma

Motzer RJ, Mazumdar M, Bacik J, et al.
J Clin Oncol. 1999;17:2530-2541.

Prognosis of RCC is primarily determined by tumor size, nuclear grade, and stage.[1] During the last decade, tumors have been discovered earlier, and innovative, immune-based treatments have become available for advanced disease. Updated information on prognostic factors for advanced cancer is clearly needed to better select patients for therapy. The authors of this paper reviewed 670 patients treated in 24 clinical trials at MSKCC between 1975 and 1996. The results provide important and interesting information regarding biology, diagnosis, and prognosis of advanced disease.

The patients were identified through registration for 24 consecutive MSKCC clinical trial programs. All patients had histologic confirmation of RCC and measurable metastatic lesions. Routine studies at the time of clinical trial entry included detailed history and physical examination, Karnofsky performance status, complete blood evaluation, and imaging studies for staging. The response to treatment, time to progression after systemic therapy, and survival were recorded. A stepwise statistical model was created to define possible prognostic factors.

Univariate and multivariate analyses were performed. Five variables were found to be significant: hemoglobin lower than the normal limit, lactate dehydrogenase higher than 300 U/L, corrected calcium higher than 10 mg/dL, absence of prior nephrectomy, and Karnofsky performance status lower than 80%. These were found to be independent risk factors for predicting survival. The highest risk ratio for mortality (× 2.52) was found to be lactate dehydrogenase at 1.5 times the upper limit or higher; the lowest risk ratio (× 1.35) was absence of prior nephrectomy.

Survival was expressed as a function of the number of risk factors each patient had (Figure). Patients with metastatic RCC who had no risk factors (25% of the study group) had 1- or 2-year survival rates of 71% and 31%, respectively. Patients with one or two risk factors (53% of the group) had 1- or 2-year survival rates of 42% and 7%, respectively. Patients with three or more risk factors (22% of the group) had a 1-year survival rate of 12%; no patient lived for 3 years.

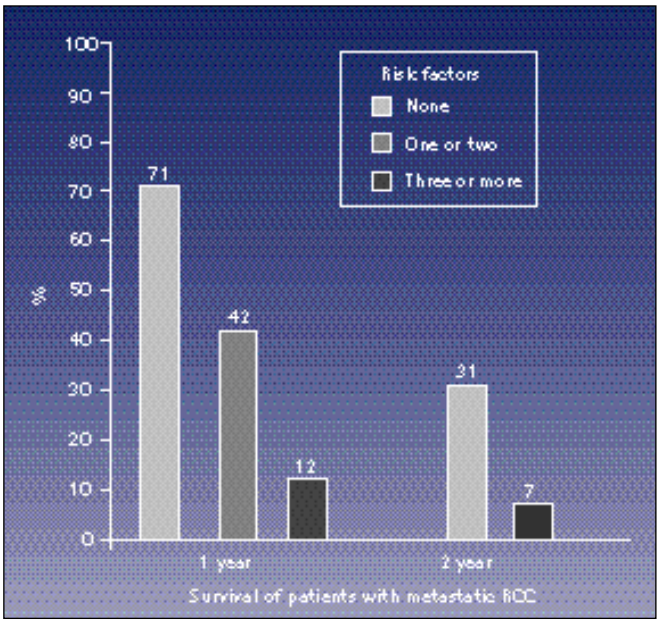

Figure. *In patients with metastatic renal cell carcinoma (RCC), certain risk factors, such as hemoglobin lower than normal, were predictive of survival.*

Overall, 59% of the group received immune-based therapy for RCC, which resulted in improved survival. For each of the three risk groups, median survival was better for patients treated recently than for those treated during the early years of the study period. Furthermore, median survival time was greater for patients treated with immunotherapy than for those treated with conventional chemotherapy. For patients treated with immunotherapy (IFN-α and/or interleukin-2), the median survival times for favorable-, intermediate-, and poor-risk patients were 26, 12, and 6 months, respectively. Moreover, when the authors applied their statistical tool to external data,[2] identical results were obtained: the median survival times of favorable-, intermediate-, and poor-risk patients were 29, 14, and 4 months, respectively.

Although lacking the uniformity of a prospective study, the results in this study are based on a solid statistical foundation. The authors supply the clinician with very simple survival predictors, based on only five clinical variables. This tool enables the physician to stratify patients. In the future, these parameters likely will be

combined with a panel of molecular markers that will better predict outcomes.

References
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2. Motzer PJ, Murphy BA, Mazumdar M, et al. Randomized phase III trial of interferon alfa-2α (IFN) versus IFN plus 13-cis-retinoic acid (CRA) in patient (pts) with advanced renal cell carcinoma (RCC). *Proc Am Soc Clin Oncol.* 1999;18:330A. Abstract 1271.

Outcome of Postchemotherapy Surgery After Treatment With Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in Patients With Unresectable or Metastatic Transitional Cell Carcinoma

Dodd PM, McCaffrey JA, Herr H, et al.
J Clin Oncol. 1999;17:2546-2552.

TCC is the most common histologic type of urothelial cancer. The sensitivity of TCC to the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) is well documented, and combination chemotherapy is the mainstay of treatment for patients with metastatic or unresectable TCC. The use of postchemotherapy surgery to resect viable residual cancer to achieve a multimodality complete response to treatment is well defined in other genitourinary malignancies. Although several studies have emphasized its value for patients in terms of improved survival and palliation of symptoms, the role of postchemotherapy surgery for TCC is not well defined. In this interesting study from MSKCC, the authors have appraised their experience with postchemotherapy surgery after M-VAC to assess its impact on survival and to better define optimal candidates for this aggressive approach.

This report is based on the retrospective analysis of 203 patients with metastatic or unresectable TCC who were treated at MSKCC with M-VAC chemotherapy as part of five trials whose results have already been reported. These trials include patients treated with standard-dose M-VAC in a phase II setting, with recombinant human granulocyte colony-stimulating factor (rh-G-CSF), with standard dose M-VAC, with dose-intense M-VAC with rh-G-CSF (phase I trial), with intermediate-dose methotrexate and standard VAC, and with dose-intense M-VAC with rh-G-CSF versus gallium nitrate plus fluorouracil (randomized trial). Inclusion criteria for these studies were similar and included the absence of brain metastasis and the documentation of adequate renal, hepatic, and cardiac function. Patients received from 1 to 12 cycles of M-VAC, and their response to chemotherapy was evaluated after every 2 cycles. Using criteria that this report does not define ("multidisciplinary evaluation of suitability was performed on a case-by-case basis"), 50 patients were selected to undergo postchemotherapy surgery after their maximum response to M-VAC was determined.

Compared with the overall cohort, the 50 patients chosen for surgery had a higher Karnofsky performance status, lower levels of alkaline phosphatase and lactate dehydrogenase, lower rates of visceral or osseous metastasis, and similar rates of lymph node involvement. They also represented a larger number of patients with unresectable primary tumors only. Furthermore, no patient with more than one anatomic site of visceral metastatic disease at baseline underwent surgery postchemotherapy. In 30 patients, a complete response was achieved using the combination of surgery and chemotherapy; of these, 10 patients (33%) are alive at 5 years, giving them a Kaplan-Meier survival estimation similar to that of the patients who achieved complete response to chemotherapy alone (41%). Subgroup analysis based on disease extent revealed that patients with unresectable primary tumors alone or with primary tumors and metastatic regional lymph nodes only responded best to multimodal therapy, with 5-year survival rates of 66% (2 of 3 patients) and 33% (3 of 9), respectively. Patients with metastases in distant lymph nodes, with visceral metastases, and with metastatic disease only responded less well. The median survival for the 30 patients with complete response was 37 months. None of the patients with lymph node involvement at the time of surgery, without a major response to chemotherapy, or without a disease-free status were alive at 5 years.

There are a number of criticisms of this study. The small size of the patient population, the retrospective nature of the analysis, the variety of chemotherapy protocols used, the variety of primary tumor sites included (bladder, renal pelvis, ureter, and urethra), and the potential selection bias inherent in the lack of prospective criteria to determine which patients would undergo postchemotherapy surgery all decrease the power of the study's findings. However, the conclusion that aggressive use of combination therapy can improve disease-free survival for carefully selected patients, particularly those with disease restricted to the primary tumor or regional lymph node sites who have achieved a major response to chemotherapy, is an important observation. The findings of this study regarding this promising therapeutic approach should be verified—via randomized, prospective trials—in terms of long-term survival, efficacy, and safety. ■